



DEFENSE HEALTH BOARD
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MAY 14 2008

DHB

MEMORANDUM FOR: The Honorable S. Ward Casscells, Assistant Secretary of Defense for Health Affairs

SUBJECT: Convalescent Plasma Therapy

1. References:

- a) Memorandum, AFEB, 18 July 2006, AFEB Select Subcommittee on Pandemic Influenza Preparedness, DoD Pandemic Influenza Preparedness Recommendations.
- b) "Open Meeting" Transcript, 12 December 2007, Defense Health Board Meeting, Arlington, Virginia.
- c) "Open Session" Transcript, 24 May 2006, AFEB Meeting, Honolulu, Hawaii.
- d) "Open Session" Transcript, 26 September 2006, AFEB Meeting, Annapolis, Maryland.
- e) DHB Select Subcommittee on Pandemic Influenza Preparedness, 27 July 2007, Pandemic Influenza Preparedness Recommendations.
- f) Memorandum, DHB, 25 September 2007, Recommendations on Southern Hemisphere Influenza Vaccine for U.S. Forces – DHB 2007-03.
- g) Presentation on Historical Use of Convalescent Plasma, Serum and Blood Products for the Treatment of Toxins and Pathogens to the DHB Subcommittee on Infectious Disease Control (IDC), 2008, by Dr. Arturo Casadevall, Albert Einstein College of Medicine-Montefiore Medical Center.
- h) Presentation on Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment to the DHB Subcommittee on IDC, 2008, by LCDR Thomas Luke, Naval medical Research Center.
- i) Presentation on the National Program to Treat Argentine Hemorrhagic Fever (Junin virus) with Convalescent Plasma to the DHB Subcommittee on IDC, 2008, by Dr. Delia Enria, Director INEVH in Pergamino, Argentina.
- j) Presentation on Human Antibody Response after Recovery from H1, H3, and H5 Influenza or Vaccination to the DHB Subcommittee on IDC, 2008, by Dr. John Treanor, University of Rochester.
- k) Presentation on Collection of Convalescent Plasma for Treatment of New, Emerging, or Biothreat Infectious Diseases to the DHB Subcommittee on IDC, 2008, by Dr. Susan Leitman, Department of Transfusion Medicine, National Institute of Health.
- l) Presentation on Convalescent Plasma Production from an Industry Perspective to the DHB Subcommittee on IDC, 2008, by Dr. Louis Katz, Mississippi Valley Regional Blood Center, Davenport, IA.

- m) Presentation on Regulatory Issues for Producing and Administering Convalescent Plasma for New and Emerging Infectious Diseases to the DHB Subcommittee on IDC, 2008, by Dr. Alan Williams, Office of Blood Research and Review (OBRR), FDA.
- n) Presentation on Clinical Guidelines, Data Collection and Reporting, and Investigational New Drug Application to the DHB Subcommittee on IDC, 2008, by Dr. Stephen Hoffman, Protein Potential LLC.
- o) Presentation on Cumulative Number of Confirmed Human Cases of Avian Influenza A(H5N1) Reported to WHO, 05 March 2008, World Health Organization.
- p) Adenovirusus. Centers for Disease Control and Prevention: National Center for Infectious Disease, Respiratory and Enteric Viruses Branch. January 21, 2005. Available at <http://www.cdc.gov/ncidod/dvrd/revb/respiratory/eadfeat.htm>. Accessed March 7, 2008.
- q) Luke et al. Meta-analysis: convalescent blood products for Spanish influenza: a future H5N1 treatment? *Annals of Internal Medicine* 2006; 145: 599-609.
- r) Zhou et al. Treatment with convalescent plasma for influenza A (H5N1) infection. *NEJM*, 2007; 357: 1450-1451.
- s) Kong and Zhou. Successful treatment of avian influenza with convalescent plasma. *Hong Kong Medical Journal* 2006; 12: 489.
- t) Russell, KL et al., Vaccine-preventable adenoviral therapy respiratory illness in US military recruits, 1999-2004. *Vaccine* 2006; 24(5): 2835-2842.

2. Background

In 1997, a novel influenza A/H5N1 virus strain infected Hong Kong residents exposed to poultry. In 2003, a closely related influenza A/H5N1 strain, also derived from poultry, infected residents of Hong Kong. As of March 2008, the World Health Organization reported 357 cases and 235 deaths in humans across 14 countries. More importantly, the virus in poultry and wild birds has continued to mutate and evolve such that several diverse clades are now apparent.

3. Chronology of Subcommittee's Consideration of Convalescent Plasma Therapy

In past influenza virus threats (eg: 1957, 1968, and 1976), the Department of Defense (DoD) was directly involved with the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) in developing and evaluating surveillance and epidemiologic data, vaccine selection, evaluating vaccine immunogenicity and reactogenicity, as well as performing vaccine efficacy studies. In the 1980s, the DoD began to play a less active role in national influenza vaccine research and development. In 2005, prompted by Secretary Winkenwerder, a subcommittee was formed under the previous Armed Forces Epidemiological Board (AFEB) to advise Surgeons Generals and other DoD members on matters relating to pandemic influenza (PI), including providing recommendations for optimizing surveillance and preparation.

The newly formed AFEB's Select Subcommittee on Avian Influenza/Pandemic Influenza (AI)/(PI) Preparedness developed recommendations to address the Department's preparedness for a possible influenza pandemic. Scenarios were provided to prompt development of a "Play Book" of responses to situations the DoD might experience in the event of a pandemic influenza.

In summary, the Subcommittee recommended stockpiling vaccines and antivirals; combining antivirals in the event of resistance; creating a “business model” to acquire vaccines as a rolling inventory; and the use of masks for persons occupationally exposed, symptomatically ill and pre-exposed. The Subcommittee further advised the DoD to serve as a full working partner with other leading public health institutions to enhance surveillance, develop a “surge capacity” in the face of an outbreak, and vaccinating household members of military personnel such as children, who are at greater risk of infection and transmission of the virus to others.

In May and June 2007, the Defense Health Board (DHB) Subcommittee on Pandemic Influenza Preparedness met and submitted recommendations to the full DHB in a memorandum of July 27, 2007. The Subcommittee recommended to Dr. Casscells, Assistant Secretary of Defense (Health Affairs), that the Department further consider the use of convalescent and immune plasma for PI and other military disease threats.

Convalescent plasma, which delivers passive antibodies from disease-specific survivors, arose as a plausible alternative therapy in the event of PI. Dr. Thomas Luke published a meta-analysis evaluating eight studies that demonstrated a significantly reduced case fatality and morbidity for patients treated with convalescent plasma therapy during the Spanish Flu era (1918-1925)⁹. This evidence was further strengthened by two independent Chinese studies showing persons infected with H5N1 resolved their influenza infections after receiving convalescent plasma therapy despite Oseltamivir resistance ¹⁰. Additionally, convalescent plasma therapy has been reported to have been effective for prophylaxis and/or treatment of several other human diseases, including Argentine hemorrhagic fever, rabies, measles, hepatitis B, cytomegalovirus, respiratory syncytial virus (RSV), and possibly severe acute respiratory syndrome (SARS) .

The rationale for the DoD to consider use of the convalescent plasma alternative is that: 1.) Active Duty personnel are at high risk for exposure to natural or bioterror infectious disease epidemics, 2.) the DoD has the capability to collect, produce, and transfuse large volumes of convalescent plasma from military volunteers who have recovered or have been vaccinated, and 3.) convalescent plasma can be used within the DoD and/or civilian populations.

Because of limited H5N1 vaccine production, acquired resistance to Oseltamivir and other antivirals, and the possibility that a different influenza strain may emerge as the pandemic strain, the use of convalescent plasma therapy and its applications for pandemic influenza were considered by members of the DHB Subcommittee.

On 5-6 February 2008, the DHB Subcommittee on PI Preparedness met to consider guidelines on the use of convalescent and immune plasma, particularly in the event of PI or other military-relevant diseases. A follow up Subcommittee teleconference was held on 20 February 2008. The Subcommittee provides the following recommendations to the DHB for consideration on convalescent plasma therapy guidelines.

4. National Effort

The Subcommittee concludes that a national effort is essential to explore convalescent plasma therapy as an adjunct treatment. The DoD, in its national security role, has a stake in ensuring guidelines and infrastructure are in place within the Department if use of convalescent plasma is needed. The Subcommittee further concludes that within the national context of an approach to convalescent plasma therapy, the DoD is not and should not lead the effort, but the DoD has a vital stake and interest in acting as a co-partner with other national health organizations such as the CDC, the Department of Homeland Security (DHS), and the NIH.

In preparing these recommendations, the Subcommittee has engaged in regular discussions and has received a series of briefings by experts from the NIH, the CDC, the National Vaccine Program Office, the FDA, and the DoD, among others. **The Subcommittee urges the DoD to consider development of convalescent plasma therapy as part of the national pandemic influenza plan, and as an important adjunct with other treatments. The Subcommittee further emphasizes the development of convalescent plasma therapy is a national effort and the Department should co-partner on this issue with other leading national health organizations.**

5. Recommendations

The Subcommittee presents the following recommendations for the Board's consideration in two parts: the first set of recommendations applies to a national-level approach for implementing convalescent therapy. The second set of recommendations includes items where the DoD should directly engage.

5.1 National-level Recommendations

- 5.1.1 *Immediate Actions*** – The Subcommittee recommends publication of a peer-reviewed article addressing alternative therapies for pandemic influenza with a focus on convalescent plasma therapy. Members of the DoD may collaborate on this effort. The article should describe established knowledge and current gaps, and provide guidance and awareness on convalescent plasma therapy to healthcare communities at a national level.
- 5.1.2** The Subcommittee recommends the national plan include establishing regional blood banks as a control point for plasma collection to ensure availability. As capabilities to accomplish this are outside the scope of the DoD, the Blood Program Office should interface with appropriate government agencies to develop the regional blood bank concept.

These high priority guidelines should address more efficient plasma screening methods that require less time during a pandemic. The DoD and the FDA should engage in dialogue to determine the minimal amount of screening that can be performed per individual and still ensure an adequate amount of safety to the recipient and donor.

5.1.3 Standardized Guidelines – The Subcommittee recommends the DoD act as a vested partner with other leading national public health institutions to contribute to the development of national standardized guidelines for use of convalescent plasma therapy as an alternative for use in pandemic influenza. The standardized guidelines for “normal” circumstances should be based on the following assumptions: (1) current antivirals will be ineffective due to resistance in individuals; (2) plausibility of a different influenza strain aside from H5N1 becoming the pandemic strain; and (3) limited vaccine distribution due to production, logistics, and healthcare delivery restrictions. The guidelines should take the form of a two part document, with the first part being general recommendations, and the second part consisting of appendices containing current knowledge, research, literature, and data on relevant infectious agents. Furthermore, the document should be made public to inform and provide assistance to healthcare professionals. The guidelines should be peer-reviewed and be updated with new data and information as needed.

5.1.4 Investigational New Drug (IND) – The Subcommittee recommends investigating further applications of convalescent plasma therapy for other infectious diseases where there is no known alternative therapy, working in partnership with the CDC, the NIH, the Office of the Assistant Secretary for Preparedness and Response (ASPR), and local blood carriers. Outside of adenoviruses, for which the DoD should be the lead in establishing the IND, the DoD should partner with other public health and research institutions to provide suggestions, direction, and support in pursuit of finding further applications of convalescent plasma therapy. Persons with severe, morbid seasonal influenza were discussed as potential research subjects for determining the effectiveness of convalescent plasma therapy. However, the Subcommittee acknowledges there are several ethical issues in the use of convalescent plasma therapy for such individuals when antivirals for seasonal influenza are available.

5.1.5 Identify Current Knowledge and Gaps in the Use of Convalescent Plasma (including Collection, Distribution, and Tracking) for different Pathogens - The Subcommittee recommends that an interagency group, including the DoD, investigate potential gaps in the infrastructure for plasma collection, distribution and tracking in the military and civilian sectors. Possible assistance may come from the Plasma Protein Therapeutics Association (PPTA), and local and commercial blood centers. The Subcommittee concludes that a meta-analysis of previous studies would identify gaps in the science. The assistance of the Uniformed Services University of the Health Sciences (USUHS) should be sought to facilitate this time- consuming inter-agency effort with other leading health and research organizations.

5.2 DoD-Relevant Recommendations

5.2.1 Adenovirus as a Model – The Subcommittee recommends the DoD evaluate convalescent plasma therapy use for serious adenovirus infections specifically and as a model for PI. Adenovirus types 4 and 7 cause acute respiratory disease (ARD) among military recruits and personnel, and on occasion, cause significant morbidity and mortality in this population. Vaccines were developed for Adenovirus serotypes 4 and 7 and were

distributed from 1970 to 1999 but the vaccine was later discontinued and adenoviral-related illnesses have since risen⁴. Like influenza, adenovirus produces similar respiratory symptoms and illness and antivirals have been shown to be ineffective. The DoD should initiate a research effort to provide data and information about the effectiveness of convalescent plasma therapy, logistical processes, and appropriate equipment.

5.2.2 Identify Gaps in Capabilities within DoD – The Subcommittee recommends the DoD search for gaps in the infrastructure for plasma collection, distribution and tracking that exists in the Services. The DoD is capable of collecting, producing, and transfusing large volumes of convalescent plasma from military volunteers who have either recovered from a disease or have been vaccinated. Convalescent plasma at the local Military Training Facility (MTF) level could potentially have some limited local impact during the next pandemic influenza if no good treatment exists.

6. Future Application of Guidelines for Emerging and Novel Agents and Biothreats

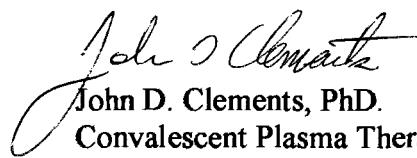
Convalescent plasma therapy has been used successfully in the past for diseases when there was no known alternative therapy; the Subcommittee urges the DoD to consider guidelines beyond pandemic influenza and to consider convalescent plasma therapy as an alternative treatment for novel, natural or man-made bio-agents and/or novel, emerging biological threats in future research and practice. Currently, the USAMRIID is investigating convalescent plasma therapy for agents posing biological threats; the Subcommittee advocates investigation and research by other organizations into utilization of convalescent plasma therapy for efficacy in treatment of emerging or novel agents and biological threats.

7. The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:



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cc:

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